Pharmacokinetic Modelling of Rifampicin, Isoniazid, Pyrazinamide, and Linezolid in Central Nervous System: Insights from a Rabbit Model of Tuberculosis Meningitis

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Background and Objectives

Tuberculous meningitis (TBM) is the most devastating manifestation of *Mycobacterium tuberculosis* infection, causing high rates of mortality and disability[1].

Recommended TBM treatment is based on that of pulmonary TB, without consideration for the protective barriers that limit drug entry into the CNS, nor the disease-related physiological changes in these barriers.

Drug concentrations cannot be obtained in human CNS tissues e.g. brain, meninges, therefore, a predictive animal model of TBM would be invaluable for drug regimens optimisation[2].

Objective: To investigate the PK of rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and linezolid (LZD) in CSF and CNS tissues using a preclinical model of TBM in rabbits[2].

Methods

Study subjects: A rabbit model of TBM that recapitulates neurological and immunopathological features of human disease were used for this study[2].

Study design: Figure 1

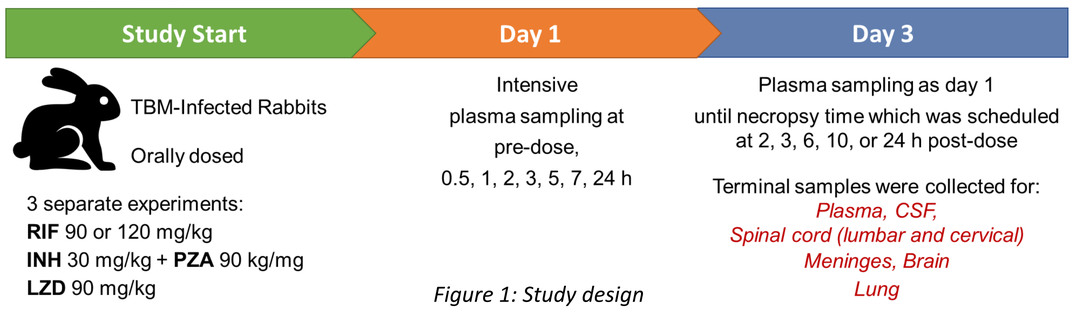
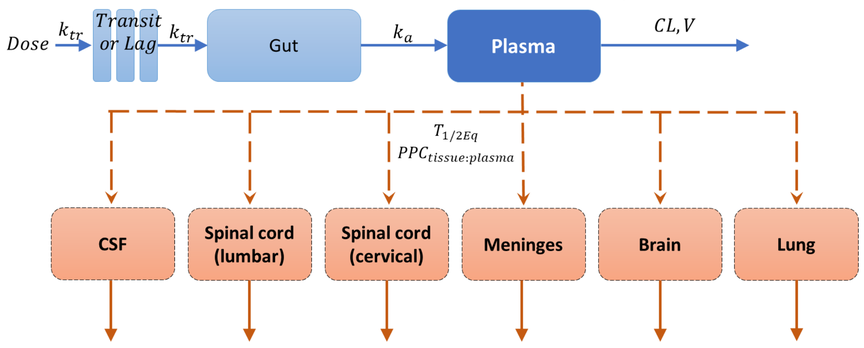


Figure 1: Study design

Drug quantification: LC-MS/MS.
LLOQs in plasma were 0.001 mg/L for RIF and LZD, 0.002 mg/L for INH, and 0.01 mg/L for PZA, while in tissues they were 0.01 mg/L for RIF, INH and LZD and 0.05 mg/L for PZA.

PopPK Modelling:
Plasma models were developed separately for each drug.
Individual plasma PK parameters (IPP) were fixed and CSF and tissue concentrations were modelled as "effect" compartments (Figure 2).



PPC: pseudo-partition coefficient (CSF or tissue to plasma drug ratio i.e. extent of drug distribution

$T_{1/2eq}$: equilibration half-life (speed of drug equilibration between plasma and CSF or tissue)

Figure 2: "Effect" compartment model diagram

Results

Observations available from both days for:
RIF: 16 rabbits (230 plasma + 155 CSF & tissue)
INH and PZA: 4 rabbits (50 plasma + 40 CSF & tissue)
LZD: 13 rabbits (117 plasma + 54 CSF & tissue)

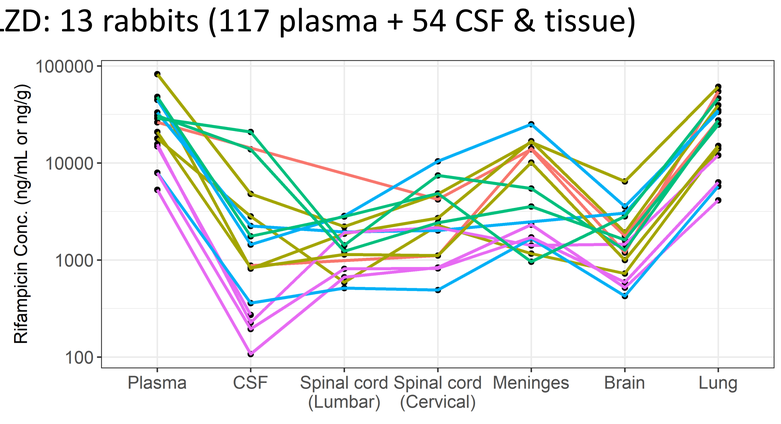


Figure 3: Matched plot for terminal plasma, CSF, and tissue rifampicin concentrations

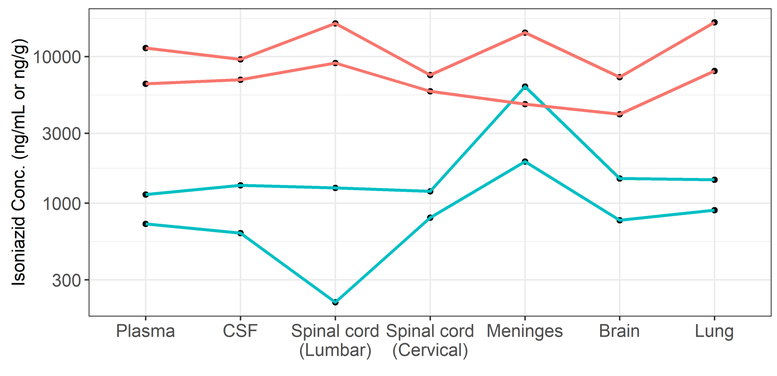


Figure 4: Matched plot for terminal plasma, CSF, and tissue isoniazid concentrations

Results *cont.*

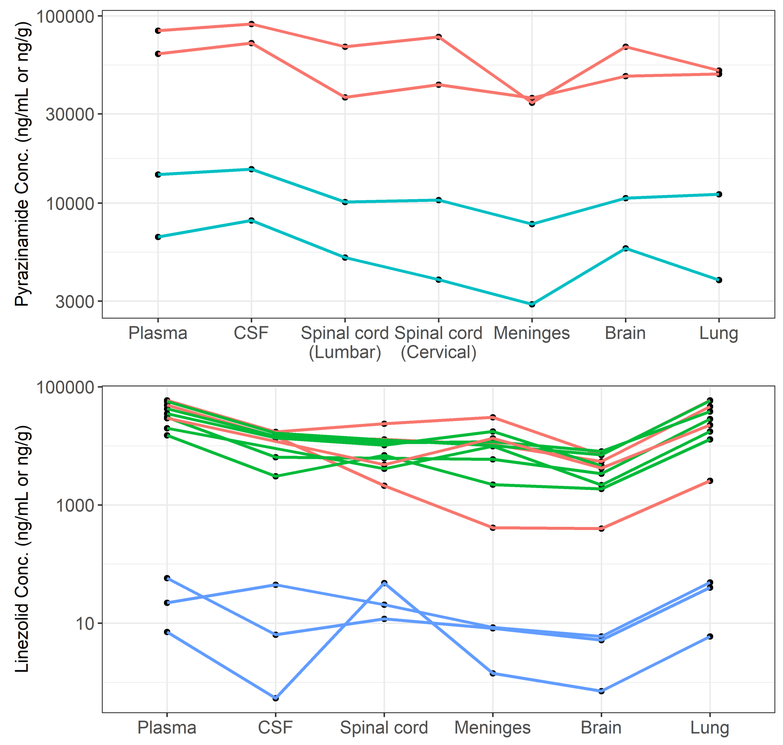


Figure 5: Matched plot for terminal plasma, CSF, and tissue pyrazinamide concentrations

Figure 6: Matched plot for terminal plasma, CSF, and tissue linezolid concentrations

Plasma PK for all 4 drugs were best described by:

- Absorption delay with transit compartments
- 1-compartment disposition model, except for INH (2-compartment)
- Allometric scaling of disposition parameters by weight

Table 1: "Effect" models parameter estimates

	CSF	Spinal cord (lumbar)	Spinal cord (cervical)	Meninges	Brain	Lung
Rifampicin						
PPC (%)	8.16 (6.84 – 10.8)	8.02 (6.95 – 9.21)	10.7 (8.44 – 13.5)	31.6 (24.3 – 41.7)	7.03 (6.56 – 7.59)	84.0 (78.2 – 90.4)
$T_{1/2eq}$ (h)	1.50 (0.584 – 2.44)	3.41 (2.41 – 5.09)	2.31 (1.47 – 3.53)	1.83 (0.916 – 3.06)	2.42 (2.08 – 2.84)	0.566 (0.202 – 0.904)
Proportional error (%)	99.7 (94.6 – 99.9)	42.7 (35.6 – 60.0)	51.1 (40.2 – 73.3)	34.4 (26.2 – 51.9)	54.7 (49.0 – 62.8)	9.73 (8.22 – 13.1)
Isoniazid						
PPC (%)	118 (80.7 - 145)	87.2 (71.3 - 110)	97.6 (71.5 - 129)	82.9 (68.2 - 103)	104 (83.7 - 124)	163 (111 - 222)
$T_{1/2eq}$ (h)	0.0592 (0.0323 – 0.241)	0.0456 (0.0264 – 0.180)	0.0257 (0.0233 – 0.0341)	0.0293 (0.0237 – 0.0537)	0.0300 (0.0239 – 0.0600)	0.601 (0.338 – 1.14)
Proportional error (%)	72.7 (44.2 – 95.6)	20.8 (12.7 – 34.3)	33.1 (19.7 – 54.4)	20.7 (12.7 – 33.5)	44.0 (32.5 – 64.9)	40.8 (22.9 – 72.6)
Pyrazinamide						
PPC (%)	106 (87.0 - 127)	69.7 (64.1 – 76.2)	76.2 (63.3 – 91.1)	47.7 (33.9 – 64.5)	74.8 (66.8 – 84.4)	66.6 (49.0 – 88.4)
$T_{1/2eq}$ (h)	0.196 (0.0957 – 0.402)	0.138 (0.0640 – 0.246)	0.0475 (0.0291 – 0.149)	0.192 (0.0909 – 0.464)	0.192 (0.0963 – 0.306)	0.187 (0.0949 – 0.462)
Proportional error (%)	18.6 (11.6 – 31.2)	5.76 (3.61 – 9.17)	18.3 (11.2 – 32.7)	31.1 (18.1 – 61.9)	19.3 (14.7 – 27.7)	28.4 (17.0 – 50.8)
Linezolid						
PPC (%)	39.1 (27.6 – 56.3)	44.3 (33.2 – 62.5)		30.5 (22.5 – 40.6)	14.9 (10.9 – 20.2)	106 (79.0 - 133)
$T_{1/2eq}$ (h)	1.25 (0.855 – 1.74)	1.22 (0.929 – 1.65)		0.543 (0.317 – 0.932)	0.849 (0.533 – 1.33)	0.684 (0.422 – 1.10)
Proportional error (%)	68.9 (47.0 – 92.8)	84.2 (62.1 – 97.8)		53.2 (36.5 – 83.8)	57.0 (38.0 – 86.4)	50.6 (34.7 – 80.1)

Values in brackets are the 95% confidence intervals obtained by sampling importance resampling
Additive error for all compartments observations was fixed to 20% of the LLOQ.
For linezolid, spinal cord tissue samples were collected without specification as lumbar or cervical

Conclusion

- A rabbit model for TBM infection[2] was successfully used to develop PK models of anti-TB drug penetration into CSF, various CNS tissues, and lungs.
- The estimated PPC and $T_{1/2eq}$ for CSF align with reports in humans[3-5], reassuring that these results could be used to predict human CNS drug levels.
- Despite limited rabbits/observations for INH/PZA, this study offers tissue observations that cannot otherwise be obtained in humans, which are invaluable to TBM treatment optimization.
- Further research is needed to establish exposure targets for optimal CNS drug levels.

Acknowledgements

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References

1. Davis AG et al. The pathogenesis of tuberculous meningitis. J Leukoc Biol. 2019;105:267–80.
2. Lanni F et al. A preclinical model of TB meningitis to determine drug penetration and activity at the sites of disease. Antimicrob Agents Chemother. 2023;67.
3. Abdelgawad N et al. Population Pharmacokinetic Analysis of Rifampicin in Plasma, Cerebrospinal Fluid, and Brain Extracellular Fluid in South African Children with Tuberculous Meningitis. Antimicrob Agents Chemother. 2023;67.
4. Ding J et al. Pharmacokinetics and Pharmacodynamics of Intensive Antituberculosis Treatment of Tuberculous Meningitis. Clin Pharmacol Ther. 2020;107:1023–33.
5. Abdelgawad N et al. Linezolid Population Pharmacokinetic Model in Plasma and Cerebrospinal Fluid Among Patients With Tuberculosis Meningitis. J Infect Dis. 2023.